REMARKS

Claims 1-2, 4-11, 14, 15, and 21-29 are pending. Claims 3, 12-13, and 16-20 have been canceled by previous amendments.

Double Patenting

Claims 1, 2, 4-6, 9-11, 14, and 21-29 (Group A) are provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over the claims of copending Application No. 09/186810.

Applicants stand by the arguments advanced in Applicants' Appeal Brief.

1. Claim Rejections - 35 USC § 102(b)/103

Claims 25 and 28 (Group B) are rejected under 35 U.S.C. §102(b) as being anticipated by or, alternatively, as being unpatentable under 35 U.S.C. §103(a) over Cahalan, et al. (US 5,308,641) (Cahalan, et al.). The Examiner's Answer again cited Cahalan, et al. as anticipating the claim language wherein the human or animal tissue is used as the solid surface and that the biomolecule is one of the growth factors listed on col. 6, lines 14-16; the abstract; col. 4, lines 20-43; and col. 6, lines 8-28. The Examiner further notes that "lightly crosslinked" falls within the scope of "crosslinked".

In response to the Examiner's Answer, Applicants respectfully submit that the reference of Cahalan et al. teaches the use of an improved spacer material to improve the biocompatability of a biomaterial. The improved spacer molecule or compound is capable of attachment to a solid surface, is large enough to extend from the surface of the solid surface, and is capable of immobilizing a biomolecule or molecules. See the abstract, background of the invention, and specifically col. 2, lines 12-18. Cahalan, et al. further stresses that the spacer material intervenes between the substrate and the biologically active compound, and sometimes, a second spacer is used. See col. 4,

lines 58-60, and col. 5, lines 44-55. Applicants further submit that the Examiner has chosen to focus on the term "lightly crosslinked" by itself, apart from the detailed description of what Cahalan et. al. meant it to be. Cahalan, et al. specifies "lightly crosslinked" for achieving its objective of lightly crosslinking the polyalkylimine attached to the substrate on the one hand, and at the same time, "with sufficient aldehyde linkages at the interface between the biomolecule and the polyalkylimine to provide light crosslinking with the attached biomolecule". See col. 3, lines 10-20. The spacer between the solid surface and the biomolecule is generated in the process. Cahalan et al. also stress that in the case of coupling a cellular adhesive molecule to the treated polyalkylimine, the spacer prevents the biomolecule cellular adhesive from becoming buried in the surface and losing bioactivity. See col. 3, lines 34-65, and col.6, lines 29-51. This teaching of spacers and their uses, along with the recitation of lightly crosslinked and glutaraldehyde crosslinkers, do not teach a crosslinked tissue having an exogenous polypeptide growth factor associated therewith, and thus does not anticipate claims 25 and 28.

Further, Cahalan et al. do not teach, suggest, or motivate "crosslinked tissue" having an exogenous polypeptide growth factor associated therewith. They are concerned with enhancing the biocompatibility of a biomaterial through the use of a spacer molecule or compound. Cahalan et al. note that "the solid surface of a biomaterial is characterized as biocompatible if it is capable of functioning or existing in contact with biological fluids and/or tissue of a living organism". In addition to the detailed explanation provided by Cahalan et al. concerning "lightly crosslinked", this teaching of enhancement further teaches away from the "crosslinked" tissue of claim 25,

as the "crosslinked tissue" having the growth factor associated therewith does not require the use of a spacer for enhancing its biocompatibility. Thus, specifically with respect to the lack of motivation, Cahalan et al.'s teaching is to teach away from the invention of claims 25 and 28 and do not render them obvious.

In view of all the arguments presented, Cahalan, et al. fail to teach or motivate one to arrive at the invention of claims 25 and 28, and claims 25 and 28 are patentable over Cahalan, et al. (US 5,308,641), under 35 U.S.C. §102(b) or, alternatively, under 35 U.S.C. §103(a).

Claims 25 and 26 (Group C) are rejected under 35 U.S.C. §102(b) as being anticipated by or, alternatively, as being unpatentable under 35 U.S.C. §103(a) over Bayne, et al. (EP 0 476 983) (Bayne, et al.). In the Examiner's Answer, the Examiner asserts that the Bayne EP application discloses applying fibrin coating, prior to or in addition to the VEGF II coating, onto the surface of the fixed umbilical vein, since the tubular supports include fixed umbilical vein. The Examiner further asserts that the "artificial blood vessel", "polymeric blood vessel", and "artificial vessel" are referring to the "fixed umbilical vein" of Bayne et. al. (Page 8, line 19). Alternatively, if one does not consider the tubular supports as including umbilical cord vein, the Examiner posits that it would have been obvious to use umbilical cord vein as the tubular support.

In Applicants' Appeal Brief, Applicants stated their belief that there was a misunderstanding of the Bayne EP application by the Examiner. Applicants continue to believe this to be the case. Applicants have presented arguments in the Appeal Brief that Bayne et al. do not render claims 25 and 26 either as being anticipated or obvious. In response to the Examiner's Answer, Applicants would also like to point out that

Bayne, et al. 's teaching centered on the purification of VEGF II so that it is free of other proteins. See page 3, lines 17-43. In mentioning the uses of VEGF II, it is specifically noted that after an adequate number of endothelial cells are grown, these cells are plated on the inside surface of the fixed umbilical vein. See page 8, lines 14-19. No mention is made of a crosslinked tissue having an exogenous growth factor associated therewith in Bayne et al., despite the Examiner's assertion that Bayne et al.'s disclosure is broad, citing the use as a medicament (claim 14) or treatment for synthetic polymeric vessels (claims 16 and 17). The teaching is still centered on purification of VEGF II. There is no teaching or motivation in Bayne, et al. to arrive at the subject matter of claims 25 and 26. The Examiner is using Applicants' invention to supply the missing link to the teaching of Bayne et al. This hindsight reconstruction should not be allowed to be used to defeat the patentability of claims 25 and 26.

In view of all the arguments presented, Applicants respectfully submit that Bayne, et al. fails to teach or motivate one to arrive at the invention of claims 25 and 26 and claims 25 and 26 are patentable over Bayne, et al. under 35 U.S.C. §102(b) or, alternatively, under 35 U.S.C. §103(a).

2. Claim Rejections - 35 USC §103(a)

Claims 1-2, 4-5, and 9-11 (Group D) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. in view of Wadström (US 5,631,011).). The Examiner asserts that Bayne, et al. discloses a growth factor and fibrin with umbilical vein, and that Wadström discloses fibrin as a common biologic tissue adhesive.

Applicants have responded in detail concerning the 35 U.S.C. § 103(a) rejection based on Bayne, et al. in view of Wadström in the Appeal Brief. In response to the

Examiner's Answer, Applicants again respectfully submit that Bayne, et. al. teach the use of proteins such as fibrin to improve the attachment of cells onto an artificial surface. See page 8, lines 21-23. This teaching in Bayne, et al. does not motivate one to look for a biologic adhesive, whether it is called a fibrin adhesive or not, to attach growth factors to allograft or xenograft tissue. The deficiency in Bayne, et al. is not supplied by Wadström's teaching that fibrin glue in general is a biologic adhesive with undesirable properties. From there, Wadström goes on to teach how to improve the fibrin glue so that it does not have a low viscosity problem, and also to teach how such an improved glue promotes wound healing without scar formation or development of adhesions. See col. 2, line 65 to col. 3, line 47. Only the teaching of Applicants' invention can supply the missing link between the teachings of Bayne, et al and Wadström.

With regard to the comment of whether fibrin itself is an adhesive, Applicants respectfully submit that Wadström teaches that fibrin itself is not an adhesive. See col. 1, lines 17-28. Bayne, et al, teach that fibrin is a protein. See page 8, line 23. Other ingredients are needed to make it into an adhesive. See Wadström, col. 1, lines 19-20. This is also reinforced in the specification of the Applicants' application. See page 13, lines 19-20. Therefore, it would not be obvious to associate a polypeptide growth factor with allograft or xenograft tissue based on such teachings.

In view of all the arguments made, the teaching of Bayne, et al. and Wadström fail to motivate one to arrive at the invention of claims 1-2, 4-5, and 9-11. These claims are patentable under 35 U.S.C. § 103(a) over Bayne, et al. in view of Wadström.

Claim 29 (Group E) is rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. in view of Wadström (US 5,631,011).). In the Examiner's Answer, the Examiner asserts that since Wadström is in the same art area of vascular tissue repair as that of Bayne, et al, there is motivation for relying on Wadström.

In response to the Examiner's Answer, Applicants respectfully submit that Bayne, et al.'s teaching of plating cells onto the inside of a synthetic blood vessel does not motivate one to look for a biologic adhesive, whether it is called a fibrin adhesive or not, to attach growth factors to allograft or xenograft tissue. The deficiency in Bayne, et al. is not supplied by Wadström's teaching that fibrin is a biologic adhesive with undesirable properties. The arguments for claims 1-2, 4-5, and 9-11 also apply here. There is no suggestion in Bayne, et al. to motivate one to combine the teaching with that of Wadström. Applicants respectfully submit that according to MPEP § 2142, three criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference, or combination of references, must teach or suggest all the claim limitations. The Examiner's argument that since Wadström is in the same area of tissue repair as that in Bayne, et al. does not make out a prima facial case of obviousness, especially since the combined teachings, even if combined, do not teach, suggest or motivate the association of polypeptide growth factor with tissue. Therefore, it would not be obvious to associate a polypeptide growth factor with allograft or xenograft tissue, the subject matter of claim 29.

In view of the arguments, the combined teaching of Bayne, et al. and Wadström fail to motivate one to arrive at the invention of claim 29. Claim 29 is patentable under 35 U.S.C. § 103(a) over Bayne, et al. in view of Wadström.

Claims 6-8, 14, 15, 21-24, and 27-28 (Group F) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bayne, et al. and Wadström as applied to claims 1-5, 9-11 and 29, and further in view of Carpentier, et al. (US 4,648,881). The Examiner noted in his Answer to Applicants' Appeal Brief that the motivation was clearly set forth in the rejection as "one would be motivated to form Bayne, et al. implants into other shapes in order to make it useful in other sites and broaden its applicability".

Arguments have been presented in the Appeal Brief concerning these references. In response to the Examiner's Answer, the comments discussed above with regard to Bayne, et al. in view of Wadström also applies here. As for Carpentier, et al., the teaching is related to treatments of tissue to reduce the incidence of calcification. It fails to supply the missing link between the subject matter of claims 6-8, 14, 15, 21-24, and 27-28, and the teachings of Bayne et. al. and Wadström. As commented above, only the teachings from Applicants' invention supply the missing link.

As for the Examiner's comment that the motivation to combine is clearly set forth in the rejection, Applicants again respectfully submit that to make out a *prima facie* case of obviousness according to MPEP § 2142, the three criteria noted above must be met. Applicants submit that first, there is no such motivation in Bayne, et al. to modify its teaching. Second, there is no reasonable expectation of success since the deficiency of Bayne, et al. is not supplied by Wadström, in view of Carpentier, et al., as noted in the Appeal Brief and here. Finally, the Bayne, et al. reference, or its combination with

Wadström, in view of Carpentier, et al., do not teach or suggest all the claim limitations to render claims 6-8, 14, 15, 21-24, and 27-28, since the missing link is supplied by the Applicants' teaching, as noted before.

In view of the arguments presented, claims 6-8, 14, 15, 21-24, 27 and 28 are patentable under 35 U.S.C. §103(a) over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11 and 29, and further in view of the Carpentier patent.

Conclusion

It is submitted that this document addresses all of the relevant issues raised by the Examiner in his final rejection and the arguments put forth by the Examiner in his Answer.

For the foregoing reasons, it is requested that the Examiner reconsider the present application in view of the remarks set forth herein and withdraw the rejections.

Respectfully submitted,

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